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(54) Regulating glucose level in blood stream

(57) For the prospective automatic determination of glucose regulation parameters specific to an individual patient, blood sugar concentration values are measured and stored in a micro-computer system during continuous insulin infusion, and after the initial normal glycaemia has been reached and maintained an impulse injection of glucose is administered to the patient along with an impulse injection of insulin. After the completion of this test phase and by means of the micro-computer system the individual metabolic parameters are determined from the measured behaviour of the glucose concentration, preferably by means of a non-linear regression analysis, following which the specific individual glucose regulation parameters are calculated under various simulated stress conditions for the diabetic. Finally, the patient's glucose concentration characteristics are prospectively calculated for a wide variety of physiological situations with a simulation program.

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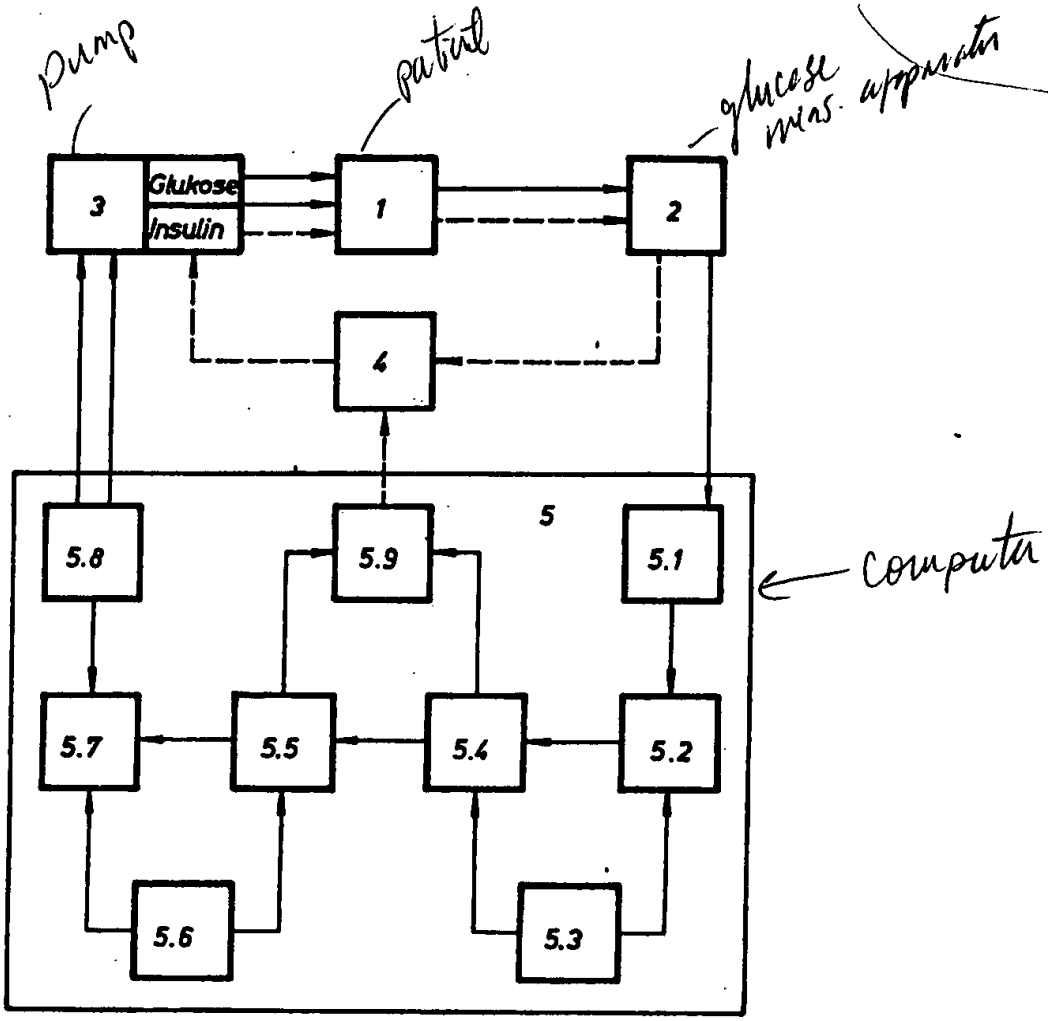

Fig. 1

SPECIFICATION

Method and apparatus for glucose regulation parameters

This invention relates to a method and apparatus for the objective automatic determination of the parameters relating to the regulation of the glucose concentration in a patient's blood for insulin thereapy in the case of diabetics using continuous insulin administration systems not controlled by feedback (open loop system) or by using an artificial beta cell, regulated by the sugar concentration of the body particularly the blood sugar (closed loop system).

Diabetes mellitus is a complex permanent metabolic disease to some extent dangerous to life, the principal sympton being increased glucose concetrations in the patent's blood stream. All forms of this condition are accompanied by a greater or lesser deficiency in the metabolic hormone "insulin". It is a known fact that the increase in glucose concentration can be counteracted by one or more daily injections of insulin from an external source other than the patient's body, thus prolonging life and working capacity for a period of years.

It is only within certain limits that the period over which the insulin is supplied and the body's continually changing insulin requirement for glucose metabolism can be properly coordinated, so there will always be a certain degree of pathological fluctuation in the glucose concentration. Over the years this will lead to irreversible secondary damage to various organs and tissues drastically reducing both the quality of life of the diabetic and his life expectancy by comparison with the average for the population as a whole.

It is nevertheless regarded as known that for the purpose of ensuring a better glucose concentration both the periods over which the secondary damage takes to appear and the degree of seriousness can be favourably controlled by adapting the insulin therapy to the metabolic characteristics of the individual diabetes sufferer. It is with this end in view that diabetics, particularly those characterized by distinct insulin deficiency accompanied by extremely unstable glucose concentration, are kept under observation as in-patients over a number of weeks, the empirical results being used retrospectively as the basis for a course of treatment of which the effectiveness is tested and if necessary re-defined after repeated re-admissions as in-patients, extending over periods of months or years. This retrospective individualization of the insulin treatment thus extends over a period of years, in addition to which it is completely dominated by empirical and subjective decisions, thus forming a strategy which at present can neither be generally adopted nor made automatic.

Methods have become known which are aimed at more rapid adaptation of insulin treatment to the individual patient on the basis of comparable observation situations and in which the daily individual changes in the patient's insulin requirements are determined under simulated domestic or occupational conditions by means of an artificial beta cell in the form of a bedside macro-apparatus, the insulin dosage profiles thus found being transferred to the injection therapy. The dosage profiles found, however, depend both on the structure of the regulating algorithms used in the system of the artificial beta cell and on the choice of the parameter values used in the said algorithms, so that different insulin dosage profiles may be found for one patient. In addition there are at present no generally binding transposition directions, that is the transposition is purely empirical, being performed on the basis of values obtained by experience, and therefore frequently has to be corrected in the light of the result of treatment, the saving of time achieved in determining the dosage profile by the use of the artificial beta cell being partly cancelled out.

In US 4146029, DE 2758467A and EU 083319 there are described insulin pump systems which can be worn or implanted and which can supply insulin in a pre-programmed or manually controllable manner to the subcutaneous tissue, the body cavities and the vascular system. It is true that these insulin pump systems enable the administration of insulin to be adapted more satisfactorily to the continually changing insulin requirements as regards time and situation, so that the fluctuations in the blood glucose concentration can be reduced. In this form of therapy likewise, however, the success of the treatment depends on the accuracy with which the preprogrammed or manually adjustable insulin administration profiles can be predicted for the individual patient concerned. Insulin pump therapy is thus subject to the same conditions as regards the individualization of the insulin dosage profiles and involves the same problems in individual adaptation as the injection therapy already discussed.

The demand for a kind of insulin administration in which the dosage will be adapted quasi-continuously to the patient's momentary needs over long periods is almost met by the artificial beta cell which is a feed-back regulating system in which the administration of insulin is controlled by a data processing unit on the basis of the continuous measement of the glucose concentration. For the known artificial beta cell systems, such as those described in FR 2298832, DD 141617 and others, in which the glucose concentration, when used for short periods ranging from a number of hours to a number of days, is almost normalized, the parameters of the control algorithms are either established in a

purely intuitive manner or else derived from the standard behaviour of the individual organism, insofar as this is already known before the onset of the diabetes. These parameters either fail to take account of the metabolic situation of the individual patient to be treated or cannot be individually predicted.

The use of artificial beta cells of this kind thus sometimes results in physiologically excessive insulin dosages, leading in their turn to pathologically excessive insulin levels in the body fluids, influencing the development of delayed complications.

A further known means for the individualization of the algorithm parameters of the artificial beta cell is the adaptive method based on a trial-and-error method and published by G. Bellomo, P. Brunetti et al, in "Optimal feedback glycaemia regulation indiabetes," Med. & Biol. Eng. & Comput., May 1982, pp. 329–335. This method, to be included in the category "retrospective individualization", like the known adaptive methods described in Bull.math. Biol. 1982 pp. 793-8-8, and MEDINFO 80, eds. A.B. Lundberg and S.Kaihara, pp. 96–100, calls for considerable expenditure on computer equipment and also proves very tim-consuming, periods ranging from a number of days to a number of weeks elapsing before the individual parameters can be obtained.

All known processes for insulin therapy thus suffer from the drawback that neither the insulin dosage profiles in "open control" nor the algorithm parameters of an artificial beta cell in "closed regulation" can be predicted and can only be adapted retrospectively to the individual metablic situation of each diabetic after the respective methods have been tried out.

An object of this invention is to determine automatically and without excesive outlay on software and hardware those glucose regulation parameters specific to an individual patient which take the insulin requirement of diabetics undergoing insulin therapy into account accurate and over a long period in accordance with the time and the situation concerned.

Thus the purpose of this invention is therefore to develop a method, and a micro-computer arrangement for the performance thereof, for the automated and objective assessment of the glucose regulation parameters specific to the individual, which can be used prospectively for the optimum application of the various forms of insulin therapy for a patient suffering from diabetes mellitus.

According to this invention this object is achieved as a result of the fact that in a test phase which lasts for several hours the blood glucose concentration values measured, particularly in the diabetic's blood circulation, are stored in an online connected micro-computer system with an integrated mathematical algorithm of a physiological glucose regulating system, and that this micro-computer system controls a complex glucose and insulin pumping system by first subjecting the patient after the initial standardization of the blood glucose concentration to a continuous insulin infusion to compensate the endogenic glucose supply and then after the maintenance of the initial standard glycaemia and preferably after about 2/5 of the test phase to an additional pulse-type insulin injection and simultaneously to an impulse-type glucose injection, and that for the subsequent test result evaluation phase the individual metabolic parameters of the diabetic are determined with the on-line coupled micro-computer system by the approximation of the glucose concentration course measured, preferably by means of a non-linear regression analysis, and that subsequently thereto the glucose regulation parameters specific to the individual are calculated by the micro-computer system, under different simulated stress conditions for the diabetic, on the basis of the course taken by the metabolism of the individual, taking account of a quality criterion, in order to minimize the deviation from normal and pathological glucose concentration, and that finally the advance calculation of the diabetic's glucose concentration characteristics is effected under a wide variety of physiological situations in accordance with a simulation program.

The automatic completion of the entire computing cycle in correct sequence, including the control operations for the course of the test, is verified in the computer system by a master program. The micro-computer system provided by the invention for the performance of the method comprises on the data input side a measured value editing module with a subsequent regression module to the output of which a model parameter computing module is connected by a first imput. Through a second input the regression module and the model parameter computing module are connected to a model system module. Furthermore, one input of an algorithm parameter computing module is connected to the first output of the model parameter computing module and the other input of the algorithm parameter computing module with the first output of a comparator module of which the first input is connected to the second output of the model parameter computing module. To the second output of the comparator module a simulator module is connected by its first input.

The second imput of the simulator module and also that of the comparator module are connected each to one output of a reference area module. To the third input of the simulator module is connected the first output of a test signal generator module of which the second and third output are connected via separate control lines to the output of the

micro-computer system with a complex glucose and insulin pump system.

The invention is further explained with reference to an Example and the accompanying schematic drawing.

Example

In the example, it is assumed that the algorithm parameter of an artificial beta cell is to be determined individually and prospectively. Fig. 1 shows the arrangement provided by the invention for automatically determining the glucose regulation parameters specific to the individual patient. According to the invention the first step in the method is the connection of the patient to be treated to the modularly constructed micro-computer system designed as a bedside apparatus for a five hour test phase. The measuring apparatus for determining the glucose concentration in the dibaetic's blood stream conveys measured values in succession to the micro-computer system in which they are intermediately stored for further evaluation. At the same time the micro-computer unit conveys control signals to a glucose and insulin pumping system connected with the patient, the said system setting up a required sequence of test signals in the pump. The test sequence according to the invention, which is started up after an initial glucose concentration standardization phase, and in which the micro-computer takes over the known function of an artificial beta cell, consists of a constant continuous insulin infusion for compensating the endogenic supply of glucose, as a result of which the initial standard glycaemia is maintained during the first two hours of the test without being controlled by measured values. An impulse-like insulin injection beginning at the third hours of the test and an impulse-like glucose injection simultaneously with the insulin is applied, the constant continuous insulin infusion being retained during the injections and in the subsequent three hours of the test. Following this test phase the patient is separated from the micro-computer system. The evaluation of the test is effected according to the invention by means of model of the physiological glucose regulating system, which is a stored system in the form of a mathematical equation system in the micro-computer system.

In the second step in the method the individual metabolism parameters of the diabetic are determined, the course taken by the glucose concentration and measured during the test being preferably approximated by means of a non-linear regression analysis in accordance with the equations of the model. From the analytical relationships between the equations of the model and the regressively determined coefficients of the approximate glucose concentration curve the glucose metabolism parameters of the individual patient can then be determined.

In the third step in the method the algorithm parameters for the artificial beta cell are determined in accordance with the glucose metabolism characteristics already determined for the individual patient, the said parameters being determined on the basis of quality criterion in such a way that the deviation between the glucose concentration calculated from the patient's model regulating circuit and that measured in normal people, are reduced to a minimum under defined stress conditions, these concentrations having been stored as reference values and reference curves in the micro-computer system.

In the fourth step in the method the patient's glucose characteristics under different physiological situations are prospectively calculated in advance, by the micro-computer system in accordance with a simulation program. The predicted glucose concentrations, the insulin dosage thereby required and the algorithm parameters of the artificial beta cell which prospectively correspond to the patient's individual metabolic situation are documentated by the micro-computer system after the completion of the fourth step in the method.

In the method according to the invention for the automated prospective determination of the specific individual, algorithm parameters of the artificial beta cell 4 (as shown in Fig. 1) the measuring apparatus 2, preferably worn or implanted in the patient 1, supplies glucose measurements continuously or in succession to a micro-computer system 5, wherein they are stored for the duration of a defined test sequence which is produced by the micro-computer system test signal generator module 5.8 for the insulin-glucose pump system 3 for the simultaneous administration of glucose and insulin.

After the completion of the test sequence, consisting of the constant insulin infusion on which the glucose injection and the insulin injection are simultaneously superimosed, the course taken by the glucose concentration and stored by the micro-computer system 5 in the measuring value preparation module 5.1 is regressively approximated in the regression module 5.2, in which process the non-linear regression equation required for the purpose is supplied by the model system module 5.3. In accordance with the analytical model equations, which supplythe relationship between the regression coefficients of the curve approximation and the parmeters of the diabetic glucose metabolism, the individual glucose metabolism parameters of the patient 1 are then determined in the model parameter calculation module 5.4. In the subsequent comparator module 5.5 the algorithm parameters of the artificial beta cell 4 related to the individual glucose metabolism parameters already determined for the patient 1 are com-

pared with the reference values or reference curves of normal people supplied as a quality criterion by the reference range module 5.6 under a defined stress condition.

The result of the adaptation of the algorithm parameters to the individual metabolism parameters of the diabetic 1 is determined by means of the simulator module 5.7, different test situations or physiological conditions being preselected for the purpose by the test signal generator module 5.8 and the simulation result being compared with known reference values and reference curves of normal people. Finally, the algorithm parameters required for the algorithms of the artifical beta cell 4 in each case are determined in the algorithm parameter calculation module 5.9.

If these algorithm parameters, by which the individual glucose metabloism situation of the diabetic 1 are taken into account prespectively, have been determined by the microcomputer system 5, they can be included in the apparatus already constructed for the artificial beta cell 4 and used for the diabetic 1, who has already been individually characterized by means of the system according to the invention.

CLAIMS

1. Method for the automatic prospective determination of glucose regulatin parameters specific to an individual patient, for supplying the insulin requirements in accordance with time and situation, in which method during a test phase the glucose concentration values measured in the patient's blood stream by means of a sensor are stored in a microcomputer system coupled on-line with a physiological glucose regulation model, a complex glucose and insulin pumping system being controlled by the micro-computer system so that after an initial standardization phase in which the micro-computer unit performs the known function of an artificial beta cell the patient's normal glycaemia is maintained by a constant continuous insulin infusion, preferably after about 2/5 of the test phase an additional impulse-type insulin injection and simultaneously therewith an impulse-type glucose injection is made the individual metabolic parameters of the patient being then determined by means of the micro-computer system by approximating the course measured for the glucose concentration and preferably using a non-linear regression analysis, the glucose regulation parameters specific to the individual patient being then calculated by the micro-computer system under simulated stress conditions for the patient, on the basis of the individual glucose metabolism characteristics already determined and taking into account a quality criterion for the purpose of minimizing the deviation between the glucose concentration calculated by the model regulating circuit for the patient and that measured in a normal person, the glucose concentration characteristics of the patient being finally calculated in advance in a wide variety of physiological situations and in accordance with a simulation program.

2. Apparatus for carrying out the method of Claim 1, characterized by the fact that a micro-computer system (5) is connected on-line to a glucose measuring device (2) in the blood stream of a patient (1), the input side of the said micro-computer system comprising a measuring value preparation module (5.1) with a subsequent regression module (5.2) to the output of which is coupled a model parameter calculation module (5.4), a model system module (5.3) being connected to the second input of the regression module and to the model parameter module, the first output of the model parameter module being connected to the first input of an algorithm parameter calculation module (5.9) and the second input of the algorithm parameter calculation module being connected to the first output of a comparator module (5.5) of which the first input is connected to the second output of the model parameter calculation module, the first input of a simulator module (5.7) being connected to the second output of the comparator module, the second input of the simulator module being connected, as the second input of the comparator module, to an output of a reference range module (5.6) and the first output of a test signal generator module (5.8) is connected to the third input of the simulator model, the second and third outputs being connected to the insulin pumping system (3).

3. A method and apparatus for determining glucose regulation parameters in a patient as herein described and exemplified.

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